

## REVIEW ARTICLE

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# Clinical Applications of Interleukin-37: A Key Player in the Immunopathogenesis of Immune Disorders

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## ABSTRACT

Recently, the era of medicine has been encountered with the exponential growth of special seroimmunobiomarkers in clinical trials. Lately, Interleukin-37 (IL-37) has attracted a wide range of basic medical scientists' attention due to its controversial functions in physiologic or pathologic microenvironments. In this research, an updated overview of immunobiological functions and clinical applications of IL-37 in a wide range of diseases, are discussed in order to highlight the role of recent laboratory-based results of IL-37.

Data of this systematic review article were collected from initial 237 articles in Google Scholar search engine, Science Direct, PubMed, Scopus, and Embase databases. Eventually, 134 total articles were considered from March 2000 to June 2019 time interval, by using 5 keywords. Relevant English articles, abstracts and conference papers all were included. No restrictions of methods and type of the article were imposed.

As one of the newly immunotherapeutic based approaches, clinical applications of cytokines are promisingly taken into account for diagnosis and treatment of multiple diseases. Various evidence suggests that IL-37 has notable roles in the regulation of acute and chronic inflammatory responses. Also, IL-37 has been studied in pregnancy, obesity, infectious, cardiovascular, neurologic, autoimmune, and metabolic diseases. Also, the protective functions of IL-37 against multiple cancers, are disputably related to the type and stage of cancer as well as the IL-37 variant.

The broad spectrum of IL-37 and its receptors in diseases, seem to be a potential candidate with pivotal effects for immunomodulation and immune gene therapy of various pathologic states.

**Keywords:** Biomarkers; Human; Immune system diseases; Immunomodulation; Immunotherapy; Interleukin-37

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## INTRODUCTION

Previously, interleukin-1 (IL-1) superfamily just consisted of interleukin-1 alpha (IL-1 $\alpha$ ) and interleukin-1 beta (IL-1 $\beta$ ). IL-1 has been called *human leukocytic pyrogen* due to its ability to induce fever.<sup>1</sup> It is also considered as one of the first lines of host defense against pathogenic organisms and tissue damages.<sup>2</sup> These days, IL-1 superfamily encompasses 4 subgroups known as (IL-1, IL-18, IL-33, IL-36) subfamilies with 11 members indicating key roles in the initiation and regulation of the immune responses in inflammatory conditions, immune-related and/or immune-mediated diseases.<sup>1,3-5</sup>

Interleukin-37 (IL-37), previously named interleukin-1 family member 7 (IL-1F7),<sup>6,7</sup> was discovered by *in silico* research in 2000<sup>4</sup> and contains 5 variants (IL-37 a-e).<sup>1,3,8</sup> The precursor of IL-37 protein weighs 30 kDa,<sup>9</sup> but the subdivisions approximately weigh 17 to 24 kDa.<sup>1</sup> IL-37b is the largest and the most studied subtype, which contains 5 exons out of 6.<sup>3,4</sup> Among five variants, only IL-37b and IL-37c comprise exon 1 and 2. Exon 1 encodes the caspase-1 cleaving site,<sup>4</sup> which shifts the precursor of IL-37b through maturation.<sup>4,8,9</sup> IL-37 is mainly expressed by peripheral blood mononuclear cells (PBMCs) like macrophages and lymphocytes in inflamed tissues.<sup>8</sup>

Regardingly, cytokines, as key immune messenger molecules in host immune system, have an important role in different inflammatory and immune-related states. The immunobiological function of cytokines in different conditions, depends on the nature of the immune mediated diseases. In other words, adjuvancy properties of cytokines is highly attributed to immunopathophysiology involved in the disease microenvironment and the subtype of the involved cytokines.<sup>10,11</sup> IL-37 is a cytokine that mediates the immune responses in adaptive and innate immunity systems.<sup>8</sup>

Most studies have focused on the anti-inflammatory roles of IL-37,<sup>7,9,12</sup> which is administrated via inhibiting the production, expression, and function of the pro-inflammatory cytokines (such as IL-1 $\alpha$ ,1 $\beta$ , 6, 8, 12, granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), tumor necrosis factor-alpha (TNF- $\alpha$ ), macrophage inflammatory protein-2 (MIP-2/CXCL2), B cell-attracting chemokine-1 (BCA-1/CXCL13), interleukine-8 (IL-8/CXCL8) and monocyte

chemoattractantprotein-5 (MCP-5/CCL12)),<sup>7,8,13-15</sup>

Recently, studies have demonstrated the multiple immunomodulatory roles of IL-37 in different inflammatory conditions, such as: infections,<sup>12</sup> immune-related diseases (including cancer<sup>16</sup>, and autoimmune diseases (ADs))<sup>17</sup>, cardiovascular diseases (CVDs) (including: atherosclerosis,<sup>18</sup> and reperfusion injury),<sup>19</sup> obesity,<sup>20</sup> pregnancy,<sup>21</sup> and some other types of diseases.

Nowadays, era of medicine has experienced substantial progress for usage of cutting-edge technologies and high-throughput techniques for diagnosis, prognosis, and treatments. Unfortunately, these recent approaches could not procrastinate the progression of mentioned diseases. As a plain truth, these mentioned diseases are accounted for high rate of morbidity and mortality, also reducing life expectancy of the patients. Thus, understanding the complete functional mechanisms of novel strategies like seroimmunobiomarkers including IL-37 and its effects on different diseases, could optimistically lead to a better control and a hopeful eradication of the diseases. Also, along with substantial progresses in omitting the science boundaries, these approaches could improve clinical outcomes through administrating novel treatment methods, such as immunotherapy or immune gene therapy for immune mediated diseases.<sup>22-29</sup>

In this review, firstly, authors try their best to provide information on the immunobiological properties of IL-37 (the structure, receptors, mechanisms of signaling, and functional roles of IL-37). In addition, they will summarize the immunomodulatory roles of IL-37 in multiple diseases and discuss the potential of IL-37-based therapeutic strategies, including IL-37 cytokine therapy and IL-37 immune gene therapy, as a new promising method for the treatment of several diseases. Such approaches may adjust laboratory-based data with clinical outcomes, and highlight the role of immunopathophysiology involved in the disease microenvironment favoring the novel viewpoints toward a more specialized medicine era. Also, they can assist medical specialists in order to reach the most precise decision to improve clinical outcomes.

## SEARCH METHOD

A global search strategy and a literature search were conducted for this present systematic review study, according to the statement related to preferred

reporting items for systematic review and meta-analysis (PRISMA) guideline.

### Literature Search Strategy

Data of this article were collected through an electronic comprehensive search strategy in Cochrane, Science Direct, PubMed, Scopus, Medline, Embase, and Google Scholar search engine/databases commencing from March 2000 to June 2019 time interval, by using 5 keywords (Biomarkers, AND Human, AND Immune System Diseases, AND Immunomodulation, AND Immunotherapy, AND Interleukin-37 protein.). Selection procedure was based on our Inclusion and Exclusion criteria as following. Generally, three independent authors measured out the first stage of data screening by a deep research into titles and abstracts of the data in order to reach to the most potentially eligible resources. On the supplementary material of data that were definitely retrieved, a manual search had been done to consider additional points. Any case of discordancy was referred to corresponding author at any stage of screening process.

### Inclusion and Exclusion Criteria

The Relevant published original (original/experimental) and review (systematic reviews/systematic review and meta-analysis/narrative reviews) data in the format of the full-text articles/abstracts/section of books/conference papers in English language that meet the criteria accordingly had been investigated in the objectives of our study, all were included. No restriction was imposed on the recruited cases of the studies (human and animal subjects) and assessed samples (blood, saliva, etc.). For the experimental studies, compared or non-compared data with control group were included. Studies with a lack of data regarding structural properties and immunomodulatory characteristics of IL-37, were not considered. Studies with ambiguous data without any described method or with insufficient data that generally were out of inclusion criteria, were totally excluded.

### Screening Process

Initially, according to keywords, 237 articles were acquired from mentioned databases/search engine. After removal of duplicate and redundant ones (n=66), title and abstract of resources from the remaining ones (n=171) were interrogated. After monitoring these

ones, the irrelevant data, data with no laboratory measurement or no prominent clinical value, and/or those which did not meet all inclusion criteria (n=47) were excluded. In a backward search among these accepted ones (n=124), an extra stage of manual searching was done on references, bibliographies and supplemental materials associated with our study in order to identify any further relevant publications and not to skip anyone. Regardingly, these additional data (n=10) were added and data of this article was eventually collected from 134 articles considering keywords, purposes, inclusion and exclusion criteria.

### Data Extraction

Two major investigators independently conducted the data extraction process. Features of every study including: name of the authors, year of the publication, journal and the diseases category were mentioned. For overlapping results or several results from one study, the authors tried their best not only cover all of the details, but also present the most complete and precise data.

According to all aforesaid criteria, studies aiming to explore the immunobiological features and clinical applications of IL-37 expression were included.

## RESULTS

### Immunobiology of IL-37

As it is mentioned earlier in purposes and search method parts of the present study, information on the immunobiological features of IL-37 (the structure, receptors, mechanism of signaling, and functional roles of IL-37) are provided here as follow:

### Receptors and Signaling

Since IL-37 and interleukin-18 (IL-18) share similar structures, extracellular IL-37b tends to bind to the  $\alpha$  chain of the IL-18 receptor (IL-18 $\alpha$ ), but with lower affinity than IL-18.<sup>1,4,6,7</sup> IL-18 induces interferon-gamma (IFN- $\gamma$ ) expression through its receptor which triggers the inflammatory responses;<sup>2</sup> however, the antagonist role of IL-18 $\alpha$  has not been clearly attributed to the attachment to IL-37.<sup>1</sup> The natural antagonist of IL-18 is IL-18 binding protein (IL-18BP). IL-37 actually binds to IL-18BP with more affinity than IL-18 $\alpha$ . This pathway majorly assists IL-37 to exert its anti-inflammatory properties.<sup>1,2,7</sup>

Intracellular IL-37 is translocated into the nucleus by Caspase-1<sup>1,8,9,12</sup> and forms a complex with small

mother against decapentaplegic homolog3 (SMAD3) to affect gene transcription procedures.<sup>1,4,7</sup> It was demonstrated that the usage of caspase-1 inhibitor in IL-37 transgenic (IL-37Tg) mice can disturb the anti-inflammatory functions of IL-37.<sup>30</sup>

IL-37 induces alterations in kinases production to make some significant changes in cellular proliferation, differentiation, and also to suppress the production of pro-inflammatory cytokines pattern. As a salient example, phosphorylation of signal transducer and activator of transcription 1 to 4 (STAT1 to 4), which has an important role in the production of inflammatory cytokines, is suppressed by IL-37. Also, IL-37 induces some modifications in P38 mitogen-activated protein kinase (MAPK), C-Jun, and P53 pathways.<sup>1</sup> In addition, with the binding of IL-37 to IL-1R8 (SIGIRR/TIR8), it competitively blocks the intracellular inflammatory pathways such as interleukin-1 receptor-associated kinase 1 (IRAK), TNF receptor-associated factor 6 (TRAF6). Altogether, these cascades eventuate in the reduction of inflammation (Figure 1). According to documents, IL-1R8 and IL-18R $\alpha$  are essential for the anti-inflammatory roles of IL-37. To sum up, IL-1R8 and IL-18R $\alpha$  form a triple ligand-receptor complex to affect several intracellular factors resulting in the inhibition of inflammation.<sup>6,12,31,32</sup>

On the other hand, it has been recently demonstrated that IL-37 increases expression of tumor growth factor-beta (TGF- $\beta$ ) by intensification of the SMAD3 pathway (an intracellular effector of TGF- $\beta$ ) as well as stimulating the TGF- $\beta$  production by CD4<sup>+</sup>/CD25<sup>+</sup> regulatory T cells (Tregs).<sup>33,34</sup> Briefly, IL-37 increases the expression of TGF- $\beta$  and reduces secretion of pro-inflammatory cytokines. Also, it suppresses the host immunity via disturbing the maturation of dendritic cells (DCs).

### Genetics

All members of IL-1 superfamily, except IL-18 and interleukin-33 (IL-33), are located on chromosome 2.<sup>2,4</sup> Accumulative studies have shown that the IL-37 gene does not exist on mice genome.<sup>2,35</sup> Two theories were suggested; it may be elsewhere in mice's genome or it has been altered during the evolutionary processes on IL-1F locus 2. IL-37Tg mice experience lower levels of hypothermia, metabolic acidosis, and liver damage in comparison with wild-type. This subject implies the protective effects of IL-37 by IL-37Tg mice against

lipopolysaccharide (LPS)-induced shock, also against colitis, spinal cord injury (SCI), Ischemic heart disease, and Metabolic syndrome.<sup>36</sup> Moreover, IL-37 gene is conserved in human and gorilla; however, it is absent in chimpanzee and bonobo.<sup>2</sup> Recently, a research group of translational transplant studies represented that some plants have significant potential to be used as a practical vector for the production of biologically active form of IL-37.<sup>37</sup>

Genetically, IL-37 has five isoforms that are expressed in different tissues<sup>2</sup> (Table1).

### Biological Role

In the absence of any exposure stimulation, the level of IL-37 expression is measured via immunocytochemical staining with a polyclonal antibody against IL-37. Immunological measurements have shown a correlation between the levels of IL-37 and inflammation. Also, it has been demonstrated that the majority of IL-37 expression occurs in the cytoplasm and granules of monocytes.<sup>2</sup>

On the whole, IL-37 is mainly expressed in the inflamed macrophage cell line in trace amounts.<sup>8</sup> However, the expression of IL-37 protein rises dose-dependently following stimulation with TGF- $\beta$  and ligands for toll-like receptors (TLRs), such as Pam<sub>3</sub>, CSK<sub>4</sub>, and LPS.<sup>1,8</sup> Also, pro-inflammatory cytokines including

IL-1 $\alpha$ , 1 $\beta$ , 6, 16, 18, IFN- $\gamma$ , TNF- $\alpha$ , and TGF- $\beta$  can exacerbate the expression of IL-37 in human blood cells.<sup>1,4</sup> On the other side, cytokines for instance: IL-4 and GM-CSF, demonstrate inhibitory effects on the activation of IL-37.<sup>1</sup> Moreover, the expression of IL-37 by PBMCs was decreased by the administration of siIL-37 or scrambled siRNA.<sup>4</sup>

As it was declared earlier, the anti-inflammatory roles of IL-37 is already proved. IL-37 majorly reduces inflammation through diminishing the expression of pro-inflammatory cytokines, such as IL-1 $\beta$  and TNF- $\alpha$ . Also, it decreases the amount of leukocyte recruitment into the inflamed site.<sup>8</sup>

Subsequently, IL-37 is a promising target for the treatment of inflammatory diseases.<sup>8,9</sup> DCs are considered as special and potential antigen-presenting cells (APCs) that activate T cells and trigger immune responses. In the inflammatory pathologic situation, inflammatory signals increase the expression of several co-stimulatory molecules (CD80, CD86, CD40) and pro-inflammatory cytokines which accelerate the activation of T cells

## Clinical Applications of Interleukin-37

**Table 1. IL-37 isoforms, component and expression sites (2)**

Name	Isoform	Component	Expression site
IL-37a	Isoform 5	exon 3, being sliced from exon 4 to 6	Brain, skin, keratinocytes, lymph nodes, bone marrow, testis, placenta, uterus, Natural Killer cells (NK), lung, monocytes, stimulated B cells, thymus, colon
IL-37b	Isoform 1	the longest variant which contains exon 1 and 2 as a prodomain and exon 4-6 in the following	Keratinocytes, skin heart, colon, lymph nodes, thymus, monocytes, placenta, uterus, bone marrow, lung, testis, NK, stimulated B cells
IL-37c	Isoform 4	exon 1 and 2 as a prodomain which is followed by exon 5 and 6	Keratinocytes, skin, lymph nodes, kidney, thymus, monocytes, bone marrow, lung, testis, placenta, colon, NK, stimulated B cells, uterus,
IL-37d	Isoform 2	exon 1 (pro-domain) which is followed by exon 4-6	Bone marrow, testis
IL-37e	Isoform 3	exon 1, 5 and 6	Bone marrow ,testis

and promote immunity functions against microbial invasion.<sup>9</sup> Several studies represented that IL-37 could modulate inflammatory conditions via disturbing DC maturation and T cell activation (Figure 1).<sup>3,4,9</sup>

Moreover, IL-37 enhances the inhibitory functions of CD4<sup>+</sup>/CD25<sup>+</sup> T regs via increase in the expression of cytotoxic T-lymphocyte-associated protein-4 (CTLA-4) and forkhead box P3 (Foxp3). Therefore, it could be possible to utilize IL-37 as an immunotherapeutic agent in ADs, sepsis, CVDs, SCI, diabetes mellitus type II (T2DM), and hepatitis.<sup>7,34</sup> With a detailed look, it is demonstrated that a group of stem cells named umbilical cord blood mesenchymal stem cells (UCB-MSCs) presented immunomodulatory and exacerbatory properties on LPS-induced IL-37 secretion in T helper cells-1 (THP-1) and macrophages through the phosphoinositide3-kinase/protein kinase B (PI3K/Akt) pathway. This function confirms the usage of mentioned cells as a new therapeutic immune cell-based strategy for the treatment of sepsis due to triggering anti-inflammatory state.<sup>38</sup> A schematic presentation related to immunomodulatory effects of IL-37 in immune system, is described in Figure 1.

In recent comprehensive studies, functions of IL-37 have been introduced controversially. It has shown both anti-inflammatory and pro-inflammatory roles which depend on the microenvironment, in which, IL-37 and related receptors are expressed. As a prime example, it has anti-inflammatory functions in inflammatory diseases and ADs. Subsequently, IL-37 has pro-inflammatory functions in pathologic conditions that

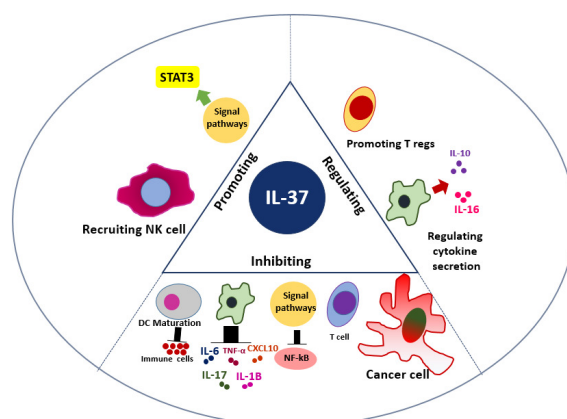
lack of inflammation in their immunopathological process.<sup>39</sup> Mechanisms related to the inflammatory roles of IL-37 will be discussed in the cancer section. Conclusively, it is of high significance to note that the role of IL-37 will be different in acute and chronic inflammation states (Figure 2).

### Immunologic Mechanisms of IL-37 Function

Table 2 indicates the immunobiological mechanisms of IL-37 function in selected pathologic conditions and microenvironments (Table 2). In the following paragraphs, exact mechanisms of IL-37 in immunopathogenesis of a wide array of immune mediated diseases in various categories are classified and discussed.

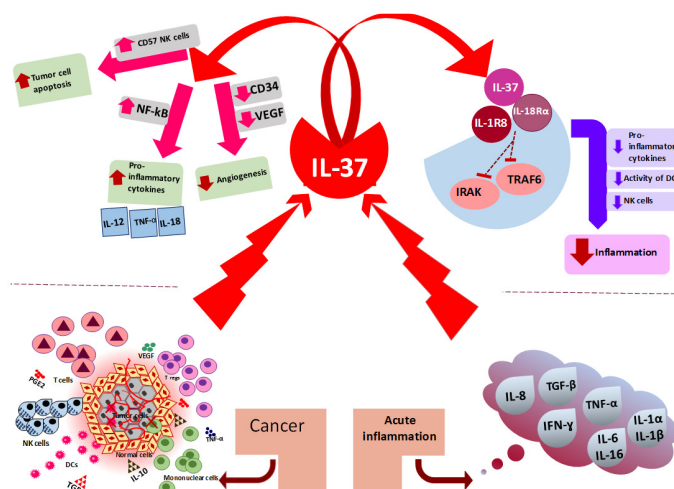
### IL-37 in Autoimmune Diseases (ADs)

Numerous evidence have proved that IL-37 has a protective role against ADs. This effect is conducted by inhibiting the production of pro-inflammatory cytokines by IL-37. Some of the inflammatory disorders and ADs that include IL-37 as part of their immunopathogenesis mechanisms, are discussed below. Although, in a most recently meta-analysis research done in a Chinese population, it has been indicated that IL-37 (rs3811047) polymorphism is involved in the progression of ADs immunopathogenesis such as ankylosing spondylitis (AS), inflammatory bowel disease (IBD), and rheumatoid arthritis (RA).<sup>17</sup>



**Figure 1.** The immunological functions of IL-37 (created by Esmailzadeh, et al). IL-37 does its immune promoting action through recruiting NK cells and some signaling pathways such as STAT3. Promoting Tregs and regulating cytokine secretion is part of the regulatory function of IL-37. IL-37 could inhibit DC maturation which can disturb the activation of immune cells and T cells. Also, IL-37 could have an inhibitory role in cancer cells. IL-37 does its inhibitory actions through some signaling pathways such as NF-κB and cytokine secretion.

Signal transducer and activator of transcription 3 (STAT3), C-X-C motif chemokine 10 (CXCL10), T regulatory cells (Tregs), Tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), DCs (DCs), Interleukin (IL).



**Figure 2.** Role of IL-37 in acute inflammation and cancer microenvironment. (Created by Esmailzadeh, et al). IL-37 could modulate inflammation in the acute phase. In the acute inflammation phase, inflammatory cytokines lead the IL-37 toward binding to its receptor. The activated signaling pathways would decrease the amount of inflammation. Also, it regulates the condition in the tumor microenvironment via the mechanisms which design in this figure. IL-37 would decrease angiogenesis, and increase tumor cells' apoptosis in the tumor microenvironment.

Transforming growth factor  $\beta$  (TGF- $\beta$ ), Natural killer cells (NK), T regulatory cells (Tregs), Interleukin-10 (IL-10), Interferon-gamma (IFN- $\gamma$ ), Tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), Prostaglandin E2 (PGE2), Interleukin-8 (IL-8), Interleukin-6 (IL-6), Interleukin-16 (IL-16), Interleukin-1 $\alpha$  (IL-1 $\alpha$ ), Interleukin-1 $\beta$  (IL-1 $\beta$ ), Vascular endothelial growth factor (VEGF), Interleukin-1 receptor 8 (IL-1R8), Interleukin-18 receptor  $\alpha$  chain (IL-18R  $\alpha$ ), Nuclear factor- $\kappa$ B (NF- $\kappa$ B), Interleukin-1 Receptor-Associated kinase 1 (IRAK), TNF receptor-associated factor 6 (TRAF6).

## Clinical Applications of Interleukin-37

**Table2. Mechanisms of IL-37 functions in selected pathologic conditions**

<b>Mechanisms of Interleukin-37 (IL-37) in different pathologic conditions</b>		
Psoriatic Arthritis	IL-37 was found in CD4 <sup>+</sup> T cells and macrophages of human psoriatic plaques. It seems that the expression of IL-37 in psoriasis is observed due to the regression of extreme inflammation.	<b>(40)</b>
Tuberculosis (TB)	Elevated IL-37 in patients with Mycobacterium Tuberculosis could be a marker for TB diagnosis.	<b>(41, 42)</b>
Aspergillosis	Injection of recombinant IL-37 could be served as a therapeutic role in the Aspergillosis-infected murine model, resulting in the inhibition of innate immunity and diminution of the pulmonary damage.	<b>(43)</b>
Atrial Fibrillation (AF)	The expression of IL-37 is related to the clinical symptoms of AF, thus, IL37 may be included as a novel target for the treatment of AF.	<b>(44)</b>
Angiogenesis	IL-37 has been introduced as a pro-angiogenic cytokine. However, the expression of IL-37 is not related to the amount of vascular endothelial growth factor (VEGF).	<b>(45)</b>
Guillain-Barre Syndrome (GBS)	High levels of IL-37 in plasma and cerebrospinal fluid (CSF) samples of GBS patients is associated with the levels of pro-inflammatory cytokines in the plasma. Moreover, the diminution of IL-37 and other cytokines was observed after Intravenous Immunoglobulin (IVIg) treatment.	<b>(46)</b>
Endometriosis	Higher expression of IL-37 has been observed in endometrial tissue which may have immunosuppressive effects via inhibition of the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling pathway. IL-37 also can be served as a diagnostic biomarker for endometriosis.	<b>(47-49)</b>
Obesity	IL-37 is involved in the differentiation of adipocytes.  IL-37 may be efficient in reducing the symptoms of diabetes type II by alteration in Insulin resistance conditions.	<b>(50)</b>
Depression	It could be beneficial as an anti-inflammatory factor and therapeutic marker for depression.	<b>(51)</b>

### **Colitis**

Intestinal epithelium expresses both pro-inflammatory and anti-inflammatory cytokines. This, creates an immune response against commensal bacteria existed in the epithelium, which finally helps to maintaining the healthy state in the intestine microenvironment. IL-37 is expressed in the intestinal epithelium, lamina propria and lymphoid cells in normal patients. Furthermore, studies demonstrated the protective roles of IL-37 against acute dextran sodium sulphate (DSS)-induced colitis.<sup>52</sup> Disturbance of the intestinal epithelium borders via bacterial invasion and inflammation, triggers the expression of IL-37 to restrict excessive inflammation.<sup>33</sup>

### **Inflammatory Bowel Disease (IBD)**

As a chronic inflammatory disease, a combination of environmental and genetic factors affect each other to begin or aggravate IBD immunopathogenesis in patients.<sup>33,53,54</sup> With the invasion of colonic epithelial cells, the microbiota reaches themselves to the basolateral membrane, where TLR5 is located. The activation of TLR5 triggers intracellular signaling pathways which lead to higher levels of IL-37 expression.<sup>13,55</sup>

Recent investigations, have represented that more IL-37-positive lymphoid cells are observed in both intestinal stainings from samples of Crohn's disease (CD) patients and ulcerative colitis (UC) patients.<sup>52-54,56</sup> As it was discussed before, IL-37 can repress inflammation via inhibition on the production of pro-

inflammatory cytokines.<sup>54</sup> Considering the method for the analysis of IL-37 expression in mentioned diseases, real-time polymerase chain reaction (RT-PCR) has been administrated for IL-37 gene expression assay. Also, immunohistochemistry and western blotting were used for analyzing the IL-37 protein expression.<sup>53,56</sup>

#### ***Autoimmune Thyroid Diseases (AITDs)***

According to the clinical manifestations, subgroups of AITDs include Grave's disease (GD) and Hashimoto's thyroiditis (HT). GD is known as the overstimulation of the thyroid gland by thyroid stimulatory antibodies. HT is a T-cell mediated disease which leads to the infiltration of the lymphocytes in the thyroid gland, destructing the thyroid gland cells. In a related study, it was represented that the minor A allele of rs3811047/rs2723176/rs2723186 and the minor G allele of rs3811046, may have a protective role against AITDs.<sup>57</sup> Also, the results of a study highlighted the direct correlation between the increased level of IL-37 expression and oxidative stress parameters that are immunopathologically counteracted in order to improve the inflammation.<sup>58</sup>

#### ***Proliferative Diabetic Retinopathy (PDR)***

PDR, as a recently autoimmune disease proved, is one of the worst complications of diabetes mellitus in which retinal ischemia causes neovascularization. PDR can lead to retinal hemorrhage, detachment, and loss of acuity and/or poor vision.<sup>59</sup> It has been interrogated that IL-37 is highly expressed in the intravitreal fluid after hypoxia. IL-37 regulates PDR by stimulating the production of VEGF-A which triggers endothelial cells (ECs) to promote angiogenesis. Additionally, there is a relation between IL-37 and the amount of angiotensin-2 (Ang-2). In conclusion, IL-37 participates in the deterioration of neovascularization process in PDR.<sup>59</sup>

#### ***Rheumatoid Arthritis (RA)***

RA is an autoimmune inflammation with long-term chronicity that primarily involves synovium and peripheral joints, subsequently developing synovial hyperplasia and pannus formation. The inflammatory reactions are associated with fibroblast like cells and cells involved in innate/adoptive immune responses. The balance between pro-inflammatory and anti-inflammatory cytokines, determines the severity of RA immunopathogenesis. Regarding the anti-inflammatory role of IL-37, it can repress the inflammatory responses

of the immune system during RA progression. IL-37 was detected in CD3<sup>+</sup> and CD4<sup>+</sup> T cells, not in CD8<sup>+</sup> T cells or CD19<sup>+</sup> B cells in RA patients. Also, the level of IL-37 expression was elevated in plasma and synovial tissue of RA patients, as well as other inflammatory cytokines. Notably, the increased level of IL-37 has a strong correlation with activated T lymphocytes that synergistically down-regulate the inflammation. Also, it was shown that increased levels of IL-37 expression are correlated with THP1/THP2/THP17-related cytokines, rheumatoid factor (RF), and anti-cyclic citrullinated peptide (ACCP). In conclusion, IL-37 can be considered as an indispensable biomarker in active RA and a pro-angiogenic factor for juvenile idiopathic arthritis (JIA). Hence, IL-37 could be a novel promising cytokine in RA seroimmunobiomarker therapy by reducing the inflammation.<sup>40,60-66</sup>

#### ***Psoriasis Vulgaris***

Psoriasis is a skin autoimmune disorder that is characterized by the infiltration of the immune cells such as DCs in skin tissues. In addition, psoriasis immunopathogenesis involves an increasing amount of chemokines production and proliferation of keratinocytes in the skin layer, following a cross-infection and an impaired immune system due to extreme DCs infiltration.<sup>67</sup> A recent study analyzed the elevated serum levels of IL-36 and IL-37 expression in psoriatic patients in comparison with healthy control. The serum levels of IL-37 was directly associated with disease severity. Thus, IL-37 could be a proficient factor for psoriasis diagnosis and treatment.<sup>68</sup>

#### ***Behcet's Disease (BD)***

As a chronic and multi-systemic inflammatory disorder, clinical manifestation of BD is accompanied with recurrent episodes of oral aphthous, genital, ocular and skin lesions, and categorized in vasculitis. Aberration in the innate/adoptive immune responses are of high importance in BD progression. Results of several studies have revealed that there is a correlation between IL-37 and uveitis in BD. A recently published study aimed at the assessment of IL-37 expression and its role in the etiopathogenesis of Behcet's disease. It is demonstrated that IL-37 is elevated in mucocutaneous tissue compared to systemic levels. It has been validated that the level of IL-37 expression is decreased in PBMCs of active BD patients. However, after the culture of monocyte-derived dendritic cells (MDCs)



with IL-37, they exhibited decreased production of IL-1 $\beta$ , 6, TNF- $\alpha$ , and increased levels of interleukin-27 (IL-27). Hence, a decreased level of IL-37 secretion may trigger the production of inflammatory cytokines through activation of Th1 and Th17 by DCs. Therefore, corticosteroid therapy can alleviate BD in inactive BD patients through the induction of IL-37, which suppresses IL-17 production and leads the microenvironment toward reduced inflammation.<sup>69-72</sup>

### ***Systemic Lupus Erythematosus (SLE)***

Being affected by several genetic predisposition and environmental determinants, SLE immunopathogenesis is involved in a multi-systemic autoimmune disease in which autoantibodies are produced against different parts of the body. This leads to the disturbance of the musculoskeletal, renal, hematologic, and central nervous system (CNS) function. It has been reported that serum levels of anti-inflammatory cytokines including IL-10, and IL-37 were high in SLE patients. However, only the levels of IL-10 were associated with disease activity. In other studies, it was demonstrated that IL-37 level is associated with disease activity, especially renal disease activity, recorded for SLE patients.<sup>73-76</sup>

### ***Multiple Sclerosis (MS)***

MS is considered as an inflammatory autoimmune disease. Cytokines play a fundamental role in this pathologic condition. Also, it was shown that expression levels of IL-33, IL-37, and plasma soluble measurable form of vascular endothelial growth factor receptor-2 (sVEGFR-2), have a correlation with the severity of MS immunopathogenesis. Another study demonstrated the correlation between the anti-inflammatory role of IL-37 in periodontal ligament cell secretome and MS.<sup>77,78</sup>

### **IL-37 in Allergy and Asthma**

#### ***Allergic Rhinitis (AR)***

AR is known as nasal mucosa eosinophilic inflammation and excessive amounts of interleukin-5 (IL-5) and immunoglobulin E (IgE) production. THP-2 cytokine pattern, plays a pivotal role in the immunopathogenesis of AR. Moreover, some factors such as major basic protein (MBP) and eosinophil cationic protein (ECP) are released from eosinophils which may lead to airway dysfunction.<sup>79</sup> IL-37 is expressed in the normal nasal mucosa, interstitial

(Testosterone producer cells in the presence of luteinizing hormone), and glandular cells. Situations, such as asthma and age, do not impact on the amount of IL-37 expression. After all, the relation between IL-37 and AR is not strong enough to be elucidated; however, its expression in nasal mucosa is a bit higher. Actually, IL-37 mediates the function of eosinophils and THP-2 products. This function leads to the modulation of the balance in the production of ECP from eosinophils and pro-inflammatory cytokines from THP-2. In addition, the expression of IL-37 is going to be diminished after steroid therapy.<sup>79</sup> In conclusion, IL-37 may regulate aberrant T cell immune responses of allergic rhinitis mainly through CD4<sup>+</sup> T cells. The immunomodulatory properties of the IL-37/IL-1R8 axis indicate the proficiency and therapeutic potentials of this axis in favor of amelioration of AR immunopathogenesis.<sup>80</sup>

A recent experimental research, has shown that intracellular IL-37b is able to reduce allergic airway hyperinflammation by affecting the human eosinophilic axis. This effect has been achieved through suppressing bacterial TLR-2-associated activation of eosinophils and also stat3/stat6 mechanisms. As a result, IL-37 could be a novel therapeutic factor in the immune gene therapy of allergic asthmatic airway disease and eosinophilic disorders.<sup>81,82</sup>

#### ***Asthma***

As a THP-2 cytokine-dependent inflammatory disorder, clinical symptoms of asthma is known by airway hyperresponsiveness and frequent episodes of broncho-obstruction which is caused by mucus overproduction that collectively is manifested by airway remodeling.<sup>83,84</sup> The main point in the treatment of asthma is suppressing the inflammation as a dominant state in airways. One of the magnificent progress in treating asthma is the usage of cytokines as seroimmunobiomarkers. Anti-inflammatory properties of IL-37 could be considered as a novel factor in asthma cytokine therapy.<sup>83,85</sup> Also, *Nina Haung*, et al, in their murine based experimental study, have determined the role of human recombinant IL-37 in the reduction of ovalbumin (OVA)-induced airway hyperresponsiveness (AHR) and inflammation by increase in IFN- $\gamma$  secretion, reduction in the levels of interleukin-4 (IL-4), IL-6, and interleukin-13 (IL-13) expression in asthma immunopathogenesis. The main aspects in immunomodulatory mechanisms of IL-37 in the hyperresponsive airway are through the inhibition

of TGF- $\beta$ 1-induced airway muscle cells proliferation, up-regulation of I kappa b (I $\kappa$ B) kinase expression, and down-regulation of NF- $\kappa$ B p65, phospho-NF- $\kappa$ B p65, STAT3, and phospho-STAT3. These alterations by administration of IL-37, totally help to asthma amelioration.<sup>86</sup>

### **IL-37 in Infectious Diseases**

#### ***Listeria Monocytogenese***

A related experimental study by Zhao et al assessed the role of IL-37 in the treatment of mice that had been infected by *Listeria Monocytogenese*. IL-37 expression induced apoptosis of macrophages and decreased macrophages number in the liver. Additionally, treatment with IL-37, could diminish bactericidal abilities of bone marrow-derived macrophages. IL-37 decelerated the production of M-CSF and GM-CSF, which act as contributing factors to granulopoiesis in acute inflammatory responses to bacterial invasion. Hence, IL -37 acted to increase the mortality rate in systemically infected mice (mice that had been infected by *Listeria Monocytogenese*).<sup>87</sup>

#### ***Candidiasis***

Other studies represented the role of human IL-37 in a murine model with disseminated candidiasis. IL-37 decreased the production of pro-inflammatory cytokines and reduced the amount of neutrophil recruitment. Thereafter, IL-37 would increase mortality rate and organ fungal growth in IL-37Tg mice infected by *C. Albicans*.<sup>88</sup>

#### ***Paracoccidioidomycosis***

Recent studies have shown the increased expression levels of IL-1 family members (IL-1 $\beta$ , IL-18, IL-33, and IL-37) in paracoccidioidomycosis patients. It seems that IL-37 is expressed in this microenvironment to decrease pro-inflammatory cytokines production and suppress the amount of inflammatory state.<sup>89</sup>

#### ***Hepatitis***

The main viral hepatic diseases include infections with hepatitis B virus (HBV) and hepatitis C virus (HCV), the two categories with the feasibility to convert into chronic hepatitis. Chronic hepatitis B (CHB) and chronic hepatitis C (CHC) may eventually lead to liver fibrosis, liver cirrhosis, and even hepatocellular carcinoma (HCC). The mechanisms of CHB and CHC are totally different. Immunocytes and

pro-inflammatory cytokines are involved in the CHB process.<sup>90</sup>

IL-1 family members seem to be involved in liver diseases as well. As mentioned earlier, one of the main roles of IL-37 is inhibiting inflammation and innate immunity in several diseases and protection from tissue injury. In a related study, aimed to investigate a link between pattern of IL-37 expression and hepatitis, level of IL-37 expression have been measured by enzyme-linked immunosorbent assay (ELISA) before and after treatment with telbivudine in CHB, CHC, and healthy control groups. The results of this study have shown that IL-37 was highly expressed in CHB and CHC before being treated with telbivudine. However, 48 weeks after treatment with telbivudine, reduction in IL-37 levels had been observed only in group of CHB patients. Thus, it can be concluded that IL-37 has a magnificent role in the immune response to HBe-Ag positive CHB, which has a direct correlation with viral load. HBV viral load is not the single factor related to serum levels of IL-37. It was shown that high levels of alanine aminotransferase (ALT) are also related to the plasma levels of IL-37.<sup>90,91</sup>

#### ***Leprosy***

Leprosy is a chronic infectious disease which is caused by *Mycobacterium leprae*. It has five clinical forms based on clinical and pathological features: tuberculoid leprosy (TT), lepromatous leprosy (LL), borderline tuberculoid (BT), borderline (BB), and borderline lepromatous (BL). Studies have demonstrated the higher expression of IL-37 in leprotic patients, which could be positively correlated with increased expression levels of caspase1, 4, MAPK, CCR6, NF- $\kappa$ B, and H $\beta$ 3. Also, the higher expression of IL-37 in endothelial cells and lymphocytes of TT in comparison with LL, might be related to the formation of new blood vessels. Totally, IL-37 seems to indicate regulatory properties for the immune cell responses, inflammation, and activity of Tregs.<sup>92</sup>

#### **IL-37 in Cardiovascular Diseases (CVDs)**

Researches have demonstrated the role of IL-37 in CVDs. It is clarified that single nucleotide polymorphism (SNP) of IL-37 has conferred a considerable risk of coronary artery diseases (CADs).<sup>93</sup> IL-37 has a major role in immunopathogenesis of multiple CVDs which are discussed below.

### ***Atherosclerosis***

As a chronic inflammatory state, atherosclerosis could be considered as a direct consequence of an imbalance between pro-inflammatory and anti-inflammatory cytokines. Also, the accumulation of multiple immune cells in the wall of the arteries is involved in the immunopathogenesis of this disease. As a matter of fact, this process leads to the formation of atherosclerotic plaques which cause an acute coronary syndrome (ACS). Both DCs and activated macrophages contribute to T lymphocytic activation. Activation of the T lymphocytes leads to the inflammation, fatty streak formation, atherosclerotic plaque formation, and thrombosis. As well as T-lymphocytes, the activated macrophages release pattern of pro-inflammatory cytokines such as IL-18, matrix metalloproteinase (MMP), and C-reactive protein (CRP), that will sensibly develop the inflammatory process.<sup>94</sup>

IL-37 treatment in apolipoprotein E (ApoE)-deficient mice, has been reported to successfully reduce the size of atherosclerotic plaque and macrophage infiltration. Former studies have represented the expression of IL-37 in foam-like cells in coronary and carotid artery plaques. Also, in atherosclerotic plaques, the expression level of IL-37 is associated with the amount of IL-18 and CRP. The common point of IL-18 and IL-37 is the administration of IL-18BP and IL-18Ra. This means that IL-37 can reduce IL-18-induced inflammation. Therefore, IL-37 may have a protective role in atherosclerotic plaques and ACS by modulating the immune cell responses. More precisely, IL-37 has potential roles in inhibition of endothelial inflammatory responses related to human coronary artery endothelial cells (HCAECs), which is associated with IL-18 signaling pathway. This, eventually promotes diminishing atherosclerotic plaques formation and refrain from subsequent adverse cardiovascular damages.<sup>95-98</sup>

Altogether, it is assumed that IL-37 exerts its anti-atherosclerotic functions in two pathways: at the molecular level, by reducing the production of inflammatory cytokines through inhibition of TLR2-NF- $\kappa$ B-ICAM-1 pathway, and in the cellular level, through inhibiting the activation of macrophages and DCs.<sup>99,100</sup>

### ***Reperfusion Injury after Myocardial Infarction (MI)***

Consecutively hypo-perfusion induced hypoxia in myocardial cells, leads the severely inflamed

microenvironment to MI. MI is a pathologic state that can cause cardiac arrhythmia, heart failure, left ventricular remodeling, and ischemia-reperfusion injury. The immunopathological mechanisms of reperfusion injury depends on the TLR signaling pathways, initiation of immunity response, and recruitment of monocytes, DCs, CD4<sup>+</sup> and CD8<sup>+</sup> T cells. This may eventually cause an aseptic inflammatory reaction.<sup>101,102</sup>

In a related study, the IL-37 treatment was introduced as a novel strategy in weakening post-MI remodeling and improving cardiac function after MI. These functions are related to the anti-inflammatory role of IL-37. IL-37 may also have a protective role in MI reperfusion injury through increasing CTLA-4 mRNA, FoxP3, and other proteins in T-regs induction, suppressing TLR-4/NF- $\kappa$ B inflammatory response in coronary artery endothelial cells, and increasing secretion of anti-inflammatory cytokines like IL-10.<sup>101,103,104</sup>

Altogether, IL-37 has a protective role in MI by reducing the size of infarction through angiogenesis and inhibition of NF- $\kappa$ B signaling.<sup>105</sup> Thus, IL-37 could ameliorate the function of cardiac muscles and decline the amount of ischemia by inhibiting the expression of inflammatory cytokines pattern and increasing the expression of anti-inflammatory cytokines pattern.<sup>19</sup>

### ***Chronic Heart Failure (CHF)***

To our knowledge, coronary diseases and myocardial infarction cause structural and functional changes in cardiomyocytes, which is called cardiac remodeling. This process can sensibly modify the left ventricular ejection fraction (LVEF). Cardiac remodeling after MI can lead to CHF. It is worthy to mention that there is a correlation between inflammatory cytokines (IL-6, IL-18, and IL-1 $\beta$ ) and cardiac remodeling. The more inflammatory cytokines exist, the more necrosis and apoptosis happen in cardiomyocytes. To draw a conclusion, IL-37 may reduce cardiac remodeling through decreasing inflammatory cytokines.<sup>106</sup>

### ***Calcific Aortic Valve Disease (CAVD)***

CAVD is a chronic inflammatory condition characterized by calcification of the cardiac valves which can eventually lead to heart failure. Based on numerous reports, expression of IL-37 in mice diminishes the stenosis of aortic valve interstitial cells

(AVICs) by increasing the serum level of osteoprotegerin (OPG).<sup>107-110</sup>

### **Coronary Artery Calcification (CAC)**

CAC is a pathological state that could concurrent with atherosclerosis or arteriosclerosis. The serum level of IL-37 is high in patients with severe CAC. It was indicated that administration of exogenous recombinant IL-37, diminishes vascular calcification by modulating the inflammatory cytokines in ApoE-deficient mice. Hence, IL-37 may be recruited as a novel predictor or therapeutic agent for CAC.<sup>105</sup>

As mentioned before, the inflammatory microenvironment can induce the expression of IL-37. As a result, IL-37 will be highly expressed in CHF. There is a direct correlation between the expression of IL-37 and hs-CRP, hs-TnT, NT-proBNP; however, and an indirect correlation between IL-37 expression, and LVEF. Thus, according to recently acquired evidence, the amount of IL-37 can be a prognostic factor in the assessment of major adverse cardiac events. No significant difference was detected between the amount of IL-37 in IHD and non-IHD and also hypertensive and non-hypertensive cardiac patients.<sup>106</sup>

### **IL-37 in Pregnancy**

One of the deteriorating events during pregnancy is pre-eclampsia syndrome, which mostly happens in the second half of pregnancy with a prevalence of 2-8%. Originating from the placenta, pre-eclampsia is clinically defined by the acute onset of hypertension and proteinuria during pregnancy. This syndrome results in the disturbance of uteroplacental perfusion, hypoxia, and oxidative stress, which can subsequently cause fetus deprivation of nutrients, hypoxia, and growth retardation. During the process, many placenta-derived factors (sIL-1RAcP, IL-18BP, IL-36Ra, and IL-37) are released into maternal blood circulation. These factors generate systemic vascular inflammation and induce the maternal immune, hormonal, and enzymatic systems. Higher levels of IL-37 and IL-18BP were detected in the pre-eclamptic placenta compared to the normal placenta. Similar to ischemia-reperfusion induced hepatitis or myocardial injury, it seems that increment in the levels of IL-37 expression in preeclampsia is associated with the hypoxic condition in the trophoblastic cell line.<sup>21</sup>

### **Gestational Diabetes Mellitus (GDM)**

Over the past few decades, frequency of GDM as intolerance response to glucose, has raised accompanied with upsurged coincidence with obesity and T2DM. According to the results of recent studies, down-regulation of IL-37 and up-regulation of IL-38 in the umbilical cord and chorionic villi are observed in GDM pregnant women compare to non-GDMs after their first trimester of pregnancy. These alterations are associated with neovascularization in neointima formation GDMs' umbilical cord and chorionic villi. Moreover, there is a negative association between IL-37 and fasting blood glucose (FBG). It has been suggested that lower amounts of IL-37 may have a contributive role in GDM progression.<sup>111</sup> MicroRNAs (miRs) have a disputable role in the pathogenesis of GDM. In a study in 2019, it has been revealed that there is a reverse correlation between IL-37 and miR-657 (stimulator of inflammatory processes). Therefore, dysregulation of miR-657 can intensify the pathogenesis of GDM.<sup>112</sup> Also, in 2018, Conti et al demonstrated that IL-37 could be beneficial for the treatment of T2DM.<sup>113</sup>

### **IL-37 in Gynecology**

#### **Adenomyosis**

Adenomyosis is the presence of endometrium in the muscle wall of the uterus (myometrium) which causes multiple complications, such as menorrhagia and dysmenorrhea. Adenomyosis is known to be a kind of inflammation defined by irrefutable evidence related to elevated levels of pro-inflammatory cytokines. It has been investigated that the expression of IL-37 will be considerably decreased in both eutopic and ectopic endometria of patients with adenomyosis.<sup>114</sup>

### **IL-37 in Neurodegenerative and Neurologic Diseases**

#### **Spinal Cord Injury (SCI)**

SCI is defined by devastating damages to the spinal cord which initiates inflammation in the neural tissue. Following inflammation, many cells and cytokines are subsequently recruited to the inflamed microenvironment. One of the cytokines that participates in this inflammatory process is IL-37. Interestingly, it has been interrogated that IL-37 has multiple roles in SCI including down-regulation of inflammation. These effects of IL-37 are specially recruited by reducing the expression of the

inflammatory genes. Also, they improve clinical outcomes by lowering neuropathic pain, enhancing myelin sparing, and protecting neurons. As a conclusion, the administration of IL-37 can be beneficial in acute SCI therapy.<sup>12,115</sup>

### ***Intervertebral Disc Degeneration***

Studies have demonstrated that there is a negative association between the expression of IL-37 and intervertebral disc degeneration. It seems that targeting IL-37 as an anti-inflammatory factor could be effective in the treatment of inter vertebral disc degeneration.<sup>116</sup>

### **IL-37 in Cancer**

Accumulative evidence has shown various roles of IL-37 in some tumor microenvironments, such as fibro carcinoma, breast cancer, and cervical cancer.<sup>22,26,39,117</sup>

### ***Mechanisms of the Function of IL-37 in Different Tumor Microenvironments***

Intracellular IL-37 suppresses tumor metastasis via inhibiting Rac1 activation. As a member of the Rho family, Rac1 is involved in different signaling pathways including modulation of cellular adhesion and polarity. It has been indicated that inhibition of the Rac1 activation by intracellular IL-37, could reduce tumor metastasis. Recent documents have represented that the existence of exogenous IL-37 in the hepatocellular carcinoma (HCC) microenvironment reduces tumor size. In addition, IL-37 may preserve healthy hepatocytes from being invaded by tumoral cells through increment in the amount of tumor-infiltrating CD57<sup>+</sup> NK cells. Also, IL-37 converts SMAD3 phospho-isoform signaling from JNK/pSmad3L/c-Myc oncogenic signaling to a tumor-suppressive pathway, pSmad3c/p21.<sup>118-120</sup>

IL-37 may have a role in the induction of autophagy (as other cytokines of IL-1 superfamily such as IL-6, IL-17A, and IL-33), apoptosis, and inhibition of tumoral cell proliferation in HCC environment. The rate of autophagosome formation inside the tumoral cells, has been shown to be increased after treatment with IL-37. Also, the partial destruction was seen with administration of 200 ng/ml IL-37 as treatment. The effect of IL-37 on autophagy is through the diminution of the mammalian target of rapamycin (mTOR) levels. As a result, IL-37 acts its role in autophagy via the mTOR/ULK1 pathway. Actually, the studies represented

the higher expression of Bax and cleaved caspase-3 and the lower expression of Bcl-2 expression. This indicates that autophagy and apoptosis occur at the same time which finally leads to the inhibition of cell proliferation and death of tumor cells.<sup>121</sup>

The inflammatory role of IL-37 in renal cell carcinoma (RCC) and non-small cell lung carcinoma (NSCLC) microenvironments is through induction of apoptosis. Also, restraining the proliferation of cancerous cells by inhibition of the IL-6/STAT3 pathway and reducing the expression of IL-6 are other mechanisms. IL-37 decreases the expression of BCL-2, cyclin-D1, and HIF-1 $\alpha$  in the tumor microenvironment. BCL-2 is a proto-oncogene that controls cell death via inhibiting apoptosis. Cyclin-D1 is a cell cycle regulator that promulgates DNA synthesis and provokes cell proliferation. HIF-1 $\alpha$  is associated with tumorigenesis, cell growth, and regulation of glucose metabolism via its correlation with related genes (VEGFA, GLUT-1). To conclude, IL-37 exerts its anti-tumoral role in the RCC microenvironment through the induction of apoptosis, deceleration of tumor cell proliferation, and reduction of tumor cell metabolism. Thus, IL-37 can be a privileged candidate in RCC and NSCLC immune gene therapy, as well.<sup>122-124</sup>

IL-37 can also depict downregulatory effects on expression of IL-6/STAT3 pathway. The tumor progression would be decreased by reducing the expression of STAT3. Moreover, epithelial to mesenchymal transition (EMT) would be decreased by reducing the expression of IL-6. Conclusively, IL-37 could act as a tumor suppressor in NSCLC. Also, the reduction in levels of CD34 is another immunomodulatory effect of IL-37 in the NSCLC microenvironment. According to the direct relation between CD34 and angiogenesis, diminution in CD34 expression will lead to decreased angiogenesis and metastasis of the tumor.<sup>39,125</sup>

IL-37 has an incontrovertible role in the activation and proliferation of CD4<sup>+</sup> T cells in the microenvironment of breast cancer; however, the correlation between IL-37 and CD8<sup>+</sup> T cells function has not been clearly demonstrated, yet.<sup>39,126</sup> In cervical cancer, IL-37 inhibits the STAT3 pathway which can eventually reduce the tumoral invasion. Furthermore, it is of high prominence to imply that the anti-tumoral function of IL-37 is dependent on the accurate activity of B and T cells.<sup>39,125-127</sup> In the colon

cancer microenvironment, the IL-37 inhibits the tumor progression via decelerating the production of IL-6 and  $\beta$ -catenin. Thus, IL-37 could be beneficially considered in immune gene therapy of colon cancer.<sup>128</sup> In addition, IL-37 could be a prognostic and diagnostic marker in oral pre-cancerous lesions. The prognostic capacity of IL-37 in pre-cancerous lesions is related to the increase in cytokine levels. Also, its diagnostic capacity is related to its diminution after transformation lesions to oral squamous cell carcinoma (OSCC).<sup>129</sup>

Some other studies in multiple myeloma (MM) demonstrated the lower levels of IL-37, which is negatively associated with the higher levels of VEGF and Ang-2. Indeed, plasma cells secrete numerous angiogenic growth factors, cytokines, MMP-2, fibroblast growth factor-2 (FGF-2), and VEGF. This will affect the angiogenesis and progression of MM immunopathogenesis. Pre-treatment with recombinant human IL-37 (rhIL-37) in human umbilical vein endothelial cells leads to the enhancement of tube formation in these cells. Thus, it was deduced that IL-37 may be an accelerating factor in MM angiogenesis and the development of the disease.<sup>130</sup>

Additionally, in another research, it was found that expression levels of CD4<sup>+</sup>CD25<sup>+</sup>Foxp3<sup>+</sup>Tregs, IL-37, and CCL22 were up-regulated in peripheral blood of lung cancer patients, which can constrain the immune response. Thus, all of the mentioned molecules, especially IL-37, could be a candidate for the diagnosis of lung cancer in early stages.<sup>131</sup>

Moreover, a related study has found high levels of IL-37 in epithelial ovarian cancer (EOC). Further studies illuminated that IL-37 has an inevitable role in tumor progression via suppressing T cell activity, disturbing the maturation of DCs, and decreasing cytokine production through down-regulating the ERK/NF-KB/S6K signaling pathway. In conclusion, the blood level of IL-37 can be a biomarker correlated with poor prognosis in EOC.<sup>132</sup>

One of the recently published studies, has demonstrated that IL-37 could be introduced as a radio-sensitizer agent in prostate cancer. IL-37 seems to be effective in radiotherapy-sensitization via inhibiting cell proliferation and enhancing cell apoptosis. Thus, the lower dosage of radiotherapy will be conducted for prostate cancer treatment which subsequently reduces the side effects.<sup>133</sup>

### **IL-37 in Periodontology**

IL-37 exists in human bio-fluids such as plasma, salivary, and gingival crevicular fluids. It has been hypothesized that the IL-37 concentration in the gingival crevicular fluid may have a role in periodontal diseases.<sup>134</sup>

### **CONCLUSION**

In spite of the fact that medicine era has been witnessed a wide array of substantial progresses, rate of morbidity and mortality of the diseases are still high and immune mediated diseases are no exception. This challenge, undoubtedly, goes back to the fact that patients suffer from either late/inaccurate diagnostic approaches or inefficient therapeutic strategies. Regardingly, this situation leads basic medical scientists toward more practical methods in order to accredit clinical outcomes. In this context, it seems that usage of seroimmunobiomarkers, can be considered as a missing piece in the puzzle of target diagnosis/therapy. To be more precise, as a well-known member of immunomodulators family in physiologic or pathologic environment, the role of cytokines including IL-37 should not be underestimated. With a comprehensive attitudes on the immunobiological functions of cytokines and their alteration involved in disease microenvironment, we can probably pave the path for promising immune gene therapeutic purposes with less side effects. As we reviewed immunobiological properties and immunomodulatory features of IL-37 in this study, we can draw a conclusion that this member of IL-1 family has a prominent regulatory role in adaptive and innate immunity responses. IL-37 affects the intracellular signaling pathways such as Smad3 and NF-kB which leads to changes in cell metabolism, function, and secretion of the cytokines by DCs. Disturbance in DC maturation and interruption in activation of immune cells, are direct consequences of IL-37 secretion. These alterations could be involved in immunopathogenesis of various diseases such as autoimmune, cardiovascular, infectious, neurologic disorders and tumor microenvironments. Therefore, IL-37 could be a novel diagnostic biomarker with significant positive predictive value and a promising therapeutic agent in immune gene therapy of numerous diseases. According to the broad spectrum

of IL-37 functions in immune mediated disorders, further investigations will be required to pale the ambiguities related to clinical application of this recently introduced biomarker. Unquestionably, correspondingly, more collaboration between medical laboratory scientists, immunologists and clinical specialists is highly recommended.

### CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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